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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/676,834	09/29/2000	Michael Z. Gilman	APBI-P04-340	4232

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EXAMINER	
SANDALS, WILLIAM O	

ART UNIT	PAPER NUMBER
1636	14

DATE MAILED: 08/13/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
09/676,834	Gilman
Examiner	**Art Unit**
William Sandals	1636

-- The MAILING DATE of this communication appears on the cover sheet with th correspondenc address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Jun 24, 2002* .

2a) ☐ This action is **FINAL.** 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under ***Ex parte Quayle***, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1-38* is/are pending in the application.

4a) Of the above, claim(s) *6-13, 16, and 21-23* is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *1-5, 14, 15, 17-20, and 24-38* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☒ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). *11*
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Election/Restriction

1. Applicant's election with traverse of Group II, claims 1-5, 14, 15 and 17-20 in Paper No. 12, filed June 24, 2002 is acknowledged. The traversal is on the ground(s) that Groups I-X should be considered as a single group since claim 1 is broader than any of the dependent claims of Groups I-X, and that the there is no search burden. This argument is found persuasive. Groups I-X are hereby rejoined into new Group I, and the claims to be examined are claims 1-5, 14, 15 and 17-20.

The requirement is still deemed proper and is therefore made FINAL.

2. Claims 6-13, 16 and 21-23 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected Groups XI-XVII, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in Paper No. 12.

Priority

3. Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 120 as follows:

An application in which the benefits of an earlier application are desired must contain a specific reference to the prior application(s) in the first sentence of the specification or in an application data sheet (37 CFR 1.78(a)(2) and (a)(5)).

Specification

4. This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the reason(s) set forth on the attached Notice To Comply With Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures. Applicant must comply with the sequence rules, 37 CFR 1.821 - 1.825. Failure to comply with these requirements will result in ABANDONMENT of the application under 37 CFR 1.821(g). Extensions of time may be obtained by filing a petition accompanied by the extension fee under the provisions of 37 CFR 1.136(a). Direct the reply to the undersigned. Applicant is requested to return a copy of the attached Notice to Comply with the reply.

5. Sequences appear in the specification at pages 43-46 without sequence identifiers.

Claim Objections

6. Claims 4, 14, 17, 18 and 20 are objected to because of the following informalities: in claim 4, "angiopoietin" is misspelled. In claim 14, "crosslinked" is misspelled. Claims 17, 18 and 20 depend from claim 16 which has been withdrawn from examination. Appropriate correction is required.

Claim Rejections - 35 USC § 112

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims 1-5, 14, 15 and 17-20 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Claims 1 and 14 have been amended to recite "ligand-crosslinked complex". There is no support in the originally filed claims or specification to support this language. Therefore, "ligand-crosslinked complex" constitutes new matter.

9. Claims 14, 15, 18-20 and 24-38 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for regulating expression of a target gene *in vitro*, does not reasonably provide enablement for regulating expression of a target gene *in vivo* which constitutes gene therapy. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. The claims are drawn to a method of regulating expression of a target gene by exposing a cell transfected with genetic constructs and a target gene to a ligand. The ligand binds to ligand binding domains in chimeric proteins expressed from the genetic constructs. While the

ligand is bound to the ligand binding domains of the chimeric proteins, the ligand-chimeric protein complex must bind to a transactivating region operatively linked to the target gene. The binding of the ligand-chimeric proteins complex to the transactivating region of the target gene regulates the expression of the target gene, both *in vitro* and *in vivo*. While applicants have shown the regulation of target genes in cells *in vitro*, they have not demonstrated any regulation of target genes in cells *in vivo*. In order to do so, undue experimentation is required. Whether undue experimentation is needed is not based on a single factor, but rather a conclusion reached by weighing many factors. Many of these factors have been summarized in *In re Wands*, 858 F.2d 731, USPQ2d 1400 (Fed. Cir. 1988).

The Wands factors as they apply to the instant claimed invention are as follows:

a- The quantity of experimentation necessary to reduce the instant claimed invention to practice would involve demonstrating that the genetic constructs can be made to express chimeric proteins which then bind to a ligand via a ligand binding domain to form a ligand-chimeric proteins complex, then the ligand-chimeric proteins complex binds to a transactivating region of a target gene in a cell *in vivo*, and thereby regulate the expression of the target gene *in vivo*.

b- Working examples of the instant claimed method have been presented for *in vitro* only.

c- No working examples of the instant claimed *in vivo* method has been provided. Limited prophetic guidance has been provided for practicing the method *in vivo*.

d- The nature of the invention is complex. Gene therapy is a new and developing art as recited in Marshall in the section titled "The trouble with vectors", and at page 1054, column 3,

and at page 1055, column 3. The problems of gene delivery, gene targeting to reach the intended host cell, and then to reach the intracellular target are not yet solved, as taught in Verma et al. (see especially page 239, column 3, the box titled "What makes an ideal vector?" and page 242).

e- The prior art taught by Orkin et al. (of record) (see especially the section on "Gene transfer and expression" and "Gene therapy in man status of the field") described many problems in the developing field of gene therapy. Recited problems include: lack of efficacy, adverse short term effects and limited clinical experience, the inability to extrapolate experimental results and unreliability of animal models. Problems with the vector include: host immune response to the vector and the expressed product, difficulty of targeting the vector to the desired site, transient expression of the gene of interest and low efficiency of delivery of the vector to the targeted site.

f- The state of the art as taught by Verma et al., which states "the problems - such as the lack of efficient delivery systems, lack of sustained expression, and host immune reactions - remain formidable problems" and Anderson, W. F. (see page 25, top of column 1), which states "[e]xcept for anecdotal reports of individual patients being helped, there is still no conclusive evidence that a gene-therapy protocol has been successful in the treatment of human disease".

g- The relative skill in the art as evidenced above, demonstrates that one of skill in the art would not know how to interpret a negative result, and thus would not know whether the method is being properly practiced as claimed without further guidance. Such guidance must be provided in the instant specification, but has not been provided.

h- Thus the practice of the instant claimed invention *in vivo* is unpredictable.

i- Therefore, given the analysis above, it must be considered that the skilled artisan would have needed to have practiced considerable non-routine, trial and error experimentation to enable the full scope of the claims.

10.The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

11. Claims 1-5, 14, 15, 17-20 and 24-38 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

12. Claim 1 and claim 14 recite a "ligand-crosslinked protein complex". This term is not defined in the claims and specification. A "ligand-crosslinked protein complex" is not an art defined term. Binding of the ligand to the chimeric proteins is taught, but crosslinking is not taught. It is not clear if the term "ligand-crosslinked protein complex" refers to a binding of the ligand to the chimeric proteins, or if it is intended to mean some other form of associating with the chimeric proteins, and as such the meaning of the term is vague and indefinite.

13. Claim 14 is drawn to a method involving regulating expression of a target protein in a cell following exposure of the cell to a ligand. There is one active step in the method, introducing genetic constructs and a target gene into a cell. There is no step for introducing a ligand to the cell, therefore, the claim lacks an active step. This lack of an active step makes the claim vague and indefinite.

Claim Rejections - 35 USC § 102

14. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless -
>
> (e) the invention was described in-
> (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effect under this subsection of a national application published under section 122(b) only if the international application designating the United States was published under Article 21(2)(a) of such treaty in the English language; or
> (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that a patent shall not be deemed filed in the United States for the purposes of this subsection based on the filing of an international application filed under the treaty defined in section 351(a).

15. Claims 1-5, 14, 15, 71-20 and 24-38 are rejected under 35 U.S.C. 102(e) as being anticipated by US 5,654,168.

US 5,654,168 teaches (see especially the summary, columns 9-15, 18, 19, 27 and 29)

a) a pair of genetic constructs encoding chimeric proteins

b) the chimeric proteins consist of a ligand binding domain and a heterologous domain

c) the chimeric proteins are expressed in a cell

d) the chimeric proteins bind to a ligand (antibiotic)

e) the ligand binding links the chimeric proteins into a multimeric complex

f) the multimeric complex binds to a transactivating region on a target gene thereby regulating the expression of the target gene, which may be an anti-angiogenesis factor (see col. 29, lines 26-55)

g) the regulation may be performed in a host organism which may be a human (see col. 27, lines 28-46)

h) the genetic constructs and the target gene may be introduced into the cell by a viral vector (see cols. 11-12)

i) numerous cell types are described (see col. 13, lines 53-64)

j) selectable markers may be used (see col. 14, lines 29-53)

k) Kd values are discussed (see col. 26, bottom)

l) ligand binding domains may be in size range of 50-350 amino acids (see column 3, lines 8-39)

The instant specification teaches anti-angiogenic factors at pages 2-3. Species of the genus of the anti-angiogenic factors are stated to be known in the prior art . The species of the anti-angiogenic factors are taught to be equivalent for the practice of the claimed invention. US 5,654168 teaches the use of anti-angiogenic factors, thereby anticipating the claimed invention.

Claim Rejections - 35 USC § 103

16. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

17. Claims 1-5, 14, 15, 17-20 and 24-38 are rejected under 35 U.S.C. 103(a) as being unpatentable over US 5,654,168 in view of WO 94/18317.

US 5,654,168 teaches (see especially the summary, columns 9-15, 18, 19, 27 and 29)

a) a pair of genetic constructs encoding chimeric proteins

b) the chimeric proteins consist of a ligand binding domain and a heterologous domain

c) the chimeric proteins are expressed in a cell

d) the chimeric proteins bind to a ligand (antibiotic)

e) the ligand binding links the chimeric proteins into a multimeric complex

f) the multimeric complex binds to a transactivating region on a target gene thereby regulating the expression of the target gene, which may be an anti-angiogenesis factor (see col. 29, lines 26-55)

g) the regulation may be performed in a host organism which may be a human (see col. 27, lines 28-46)

h) the genetic constructs and the target gene may be introduced into the cell by a viral vector (see cols. 11-12)

i) numerous cell types are described (see col. 13, lines 53-64)

j) selectable markers may be used (see col. 14, lines 29-53)

k) claimed Kd values and molecular size is taught (see col. 26, bottom)

l) ligand binding domains may be in size range of 50-350 amino acids (see column 3, lines 8-39)

US 5,654,168 does not teach the use of an immunophilin ligand binding domain, a cyclophilin ligand binding domain or a steroid receptor binding domain.

WO 94/18317 teaches (see especially pages 6-7) the equivalence of an antibiotic binding domain, a cyclophilin ligand binding domain or a steroid binding domain to practice a method of the invention. WO 94/18317 taught a method of regulating expression of a target gene by exposing a cell transfected with genetic constructs and a target gene to a ligand. The ligand binds to ligand binding domains in chimeric proteins expressed from the genetic constructs. While the ligand is bound to the ligand binding domains of the chimeric proteins, the ligand-chimeric protein complex must bind to a transactivating region operatively linked to the target gene. The binding of the ligand-chimeric proteins complex to the transactivating region of the target gene regulates the expression of the target gene, both in vitro and in vivo.

It would have been obvious to one of ordinary skill in the art at the time of filing the instant application to combine the teachings of US 5,654,168 with WO 94/18317 because they were both practicing a method of method of regulating expression of a target gene by exposing a cell transfected with genetic constructs and a target gene to a ligand. The ligand binds to ligand binding domains in chimeric proteins expressed from the genetic constructs. While the ligand is bound to the ligand binding domains of the chimeric proteins, the ligand-chimeric protein

complex must bind to a transactivating region operatively linked to the target gene. The binding of the ligand-chimeric proteins complex to the transactivating region of the target gene regulates the expression of the target gene, both in vitro and in vivo. WO 94/18317 taught the obvious use of a cyclophilin binding domain or a steroid binding domain as an obvious alternative to the antibiotic binding domain of US 5,654,168.

One of ordinary skill in the art would have been motivated to combine the teachings of US 5,654,168 with WO 94/18317 because WO 94/18317 taught the obvious alternate use of an antibiotic binding domain, a cyclophilin binding domain or a steroid binding domain for the beneficial and desirable regulation of a target gene in a cell of an animal with a small ligand molecule which will pass easily through a cell membrane to regulate the target gene. Further, a person of ordinary skill in the art would have had a reasonable expectation of success in the producing the instant claimed invention given the teachings of US 5,654,168 with WO 94/18317.

Conclusion

18. Certain papers related to this application are ***welcomed*** to be submitted to Art Unit 1636 by facsimile transmission. The FAX numbers are (703) 308-4242 and 305-3014. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 CFR 1.6(d)). NOTE: If applicant *does* submit a paper by FAX, the original copy should be retained by the applicant or applicant's representative, and the FAX receipt from your FAX machine is proof of delivery. NO

DUPLICATE COPIES SHOULD BE SUBMITTED, so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning this communication or earlier communications should be directed to Dr. William Sandals whose telephone number is (703) 305-1982. The examiner normally can be reached Monday through Thursday from 8:30 AM to 7:00 PM, EST. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel can be reached at (703) 305-1998.

Any inquiry of a general nature or relating to the status of this application should be directed to the Zeta Adams, whose telephone number is (703) 305-3291.

William Sandals, Ph.D.

Examiner

August 10, 2002

TERRY MCKELVEY
PRIMARY EXAMINER